APPENDIX D

Specification Support for Amended and Added Claims to Provoke the Interference

Claim	Support in Specification
Claim 1767. A process for detecting non-radioactively labeled nucleic acid fragments with a sequencing gel, comprising:	Support for a method of determining the sequence of a nucleic acid of interest can be found, for instance, on page 84, 2nd ¶, which states that the signaling molecules of the invention are "particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Detecting nucleic acid fragments on a sequencing gel necessarily involves determining the sequence of the fragment.
providing or generating detectable non-radioactively labeled nucleic acid fragments, wherein each of said fragments comprises one or more nucleotides,	Providing and generating labeled nucleic acid fragments complementary to the nucleic acid of interest is thoroughly discussed throughout the entire specification. In particular, U.S. Ser. No. 255,233 which eventually became the Ward Patents (e.g. 5,476,928 etc.), is incorporated in its entirety on pages 2 through 49 and is directed to non-radioactively labeled nucleic acid fragments and their complements. *See, e.g.*, the Abstract; page 6, final ¶; page 18, final ¶ through page 19, top ¶; page 28, 1st full ¶ through page 38, final ¶.
and wherein said one or more nucleotides comprise one or more fluorescent or chemiluminescent indicators on the furanosyl moiety, the phosphate moiety or the base moiety or any combination thereof;	The specification provides support for non-radioactive indicator molecules such as, fluorescent and chemiluminescent dyes including fluorescein, rhodamine and dansyl. *See, e.g.*, page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133. The specification also discloses attaching indicator molecules to the base moiety, phosphate moiety and to the sugar moiety (including furanose). *See, e.g.*, pages 93 through 95; *see also, e.g.*, page 62, example XIII; page 72, example XV; and page 73, 2nd full ¶.
subjecting said labeled fragments to a	Literal support for "sequencing gel" may be found on page 84, 2nd ¶: "This Type of self-signaling molecule can be used to monitor any nucleic acid hybridization reaction. It is

Claim	Support in Specification
sequencing gel to separate or resolve said fragments; and	particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the specification provides support for "sequencing gel," *e.g.,* page 84, which necessarily involves separating and resolving nucleic acid fragments.
detecting non-radioactively said separated or resolved fragments by detecting the fluorescent or chemiluminescent indicators.	Detecting the presence of the fragments is disclosed throughout the entire specification, such as in the Abstract, page 6 (penultimate ¶), page 84 (2nd ¶), page 93 through page 95, and original Claims 1, 7, 141, 142 and 168. The specification also provides support for detecting the nucleic acids by means of fluorescent and chemiluminescent dyes including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
Claim 1768. A process for resolving or separating non-radioactively labeled nucleic acid fragments with a sequencing gel, comprising:	Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the specification provides support for sequencing gel, *e.g.,* page 84, which necessarily involves separating and resolving nucleic acid fragments.
providing or generating detectable non-radioactively labeled nucleic acid fragments comprising one or more nucleotides that may be attached to, or coupled to, or incorporated into DNA or RNA,	Providing and generating labeled nucleic acid fragments complementary to the nucleic acid of interest is thoroughly discussed throughout the entire specification. In particular, U.S. Ser. No. 255,233 which eventually issued as the Ward Patents (*e.g.,* 5,476,928 etc.), is incorporated in its entirety on pages 2 through 49 and is directed to non-radioactively labeled nucleic acid fragments and their complements. *See also, e.g.,* the Abstract; page 6, final ¶; page 18, final ¶ through page 19, top ¶; page 28, 1st full ¶ through page 38, final ¶.
and wherein one or more fluorescent indicators are covalently attached, directly	The specification provides support for non-radioactive indicator molecules such as fluorescent dyes including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages

Claim	Support in Specification
or through a linkage group, to the furanosyl moiety, the phosphate moiety, the base moiety of said nucleotides, or any combination thereof;	46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133. The specification also discloses attaching indicator molecules to the base moiety, phosphate moiety and to the sugar moiety (including furanose), *e.g.*, on pages 93 through 95, page 62, example XIII; page 72, example XV; and page 73, 2nd full ¶.
subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and	Literal support for "sequencing gel" may be found on page 84, 2nd ¶: "This Type of self-signaling molecule can be used to monitor any nucleic acid hybridization reaction. It is particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the specification provides support for sequencing gel, e.g. page 84, which necessarily involves separating and resolving nucleic acid fragments.
detecting non-radioactively said separated or resolved fragments by means of said fluorescent indicators attached to said nucleotides.	Similarly, detecting the presence of the fragments is disclosed throughout the entire specification, such as in the Abstract, page 6 (penultimate ¶), page 84 (2nd ¶), page 93 through page 95, and original Claims 1, 7, 141, 142 and 168. Furthermore, the specification provides support for detecting the nucleic acids by means of fluorescent dyes including fluorescein, rhodamine and dansyl see, for example page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
Claim 1769. A process for determining the sequence of a nucleic acid of interest comprising:	Support for a method of determining the sequence of a nucleic acid of interest can be found, for instance, on page 84, 2nd ¶, which states that the signaling molecules of the invention are "particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Detecting nucleic acid fragments in a sequencing gel necessarily involves determining the sequence of the fragment.
providing at least one nucleic acid of	The specification provides support for providing nucleic acid sequences of interest which,

Claim	Support in Specification
interest;	when hybridized to the labeled polynucleotides of the invention, are detectable. *See, e.g.,* page 29 final ¶ through page 30, 1st ¶.
generating detectable non-radioactively labeled nucleic acid fragments complementary to said nucleic acid of interest or a portion thereof,	Providing and generating labeled nucleic acid fragments complementary to the nucleic acid of interest is thoroughly discussed throughout the entire specification. In particular, U.S. Ser. No. 255,233 which eventually issued into the Ward Patents (*e.g.,* 5,476,928 etc.), is incorporated in its entirety on pages 2 through 49 and is directed to non-radioactively labeled nucleic acid fragments and their complements. *See also, e.g.,* the Abstract; page 6, final ¶; page 18, final ¶ through page 19, top ¶; page 28, 1st full ¶ through page 38, final ¶.
wherein said fragments have been labeled by incorporation of one or more nucleoside triphosphates comprising different fluorescent indicators,	The specification provides support for nucleic acid fragments which have incorporated nucleotides labeled by one or more different fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶. "Different" fluorescent labels are specifically disclosed on page 48, 1st ¶, "If necessary, two sets of labels can be used -- one which would be specific for chromosome 23 and one for some other chromosome. By measuring in each cell the ratio of the two labels, which might be of different colors, it is possible to identify the cells which show an abnormal number of chromosomes number 23." *See also*, Example 9 on pages 46 through 47, and original Claims 42, 43, 88, 89, and 130-133 that claim fluorescein, rhodamine and dansyl.
subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and	Literal support for "sequencing gel" may be found on page 84, 2nd ¶: "This Type of self-signaling molecule can be used to monitor any nucleic acid hybridization reaction. It is particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶).

Claim	Support in Specification
detecting said separated or resolved fragments by means of said fluorescent indicators,	Detecting the presence of the fragments is disclosed throughout the entire specification, such as in the Abstract, page 6 (penultimate ¶), page 84 (2nd ¶), page 93 through page 95, and original Claims 1, 7, 141, 142 and 168. The specification also provides support for detecting the nucleic acids by means of fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.*, page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
to determine the sequence of said nucleic acid of interest.	The specification provides support for detecting fragments on a sequencing gel, *e.g.*, page 84, which necessarily includes determining the sequence of the fragment.
Claim 1770. The process according to claim 1769, wherein in said generating step, said modified or labeled nucleoside triphosphates comprise a furanosyl moiety.	*See* support for Claim 1669, above. *See also, e.g.*, pages 93 through 95; page 62, example XIII; page 72, example XV; and page 73, 2nd full ¶ (disclosing attachment of indicator molecules to furanose moiety).
Claim 1771. The process according to claim 1770, wherein said furanosyl moiety comprises a ribose, 2'-deoxyribose, 3'-deoxyribose or 2',3'-dideoxyribose.	*See* support for Claim 1770, above. *See also, e.g.*, page 62, example XIII (disclosing use of 2-deoxy-3, 5-di-O-p-toluyl-D-ribofuranosyl chloride as an intermediate in nucleotide synthesis); page 72, example XV (disclosing use of B-D-ribofuranosyl as an intermediate in nucleotide synthesis); and page 73, 2nd full ¶ (disclosing use of β-D-2-deoxyfuranosyl as an intermediate in nucleotide synthesis).
Claim 1772. The process according to claim 1769, wherein in said generating step, said different fluorescent indicators comprise fluorescein, rhodamine or dansyl.	*See* support for Claim 1669, above.

Claim	Support in Specification
Claim 1773. The process according to claim 1769, wherein in said generating step, said one or more nucleoside triphosphates comprise a base moiety or a base analog comprising a purine, a purine analog, a 7-deazapurine, a 7-deazapurine analog, a pyrimidine, or a pyrimidine analog.	*See* support for Claim 1669, above. *See also, e.g.,* pages 2 through 49, which incorporate U.S. Ser. No. 255,233 which eventually became the Ward Patents (e.g. 5,476,928 etc.), (disclosing labeled nucleosides or nucleoside analogs comprising a purine, 7-deazapurine, or pyrimidine); Specific support for "analogs" can also be found throughout the specification including, for example, page 7, 1st ¶; and page 31, 1st full ¶.
Claim 1775. The process according to claim 1773, wherein the fluorescent or chemiluminescent indicators in said modified or labeled nucleoside triphosphates are attached to said purine, said purine analog, said 7-deazapurine, said 7-deazapurine analog, said pyrimidine, or said pyrimidine analog.	*See* support for Claim 1773, above. *See also, e.g.,* pages 93 through 95 (disclosing attachment of indicator molecules to the base moiety; *see also, e.g.,* page 106-107.
Claim 1782. A process for detecting non-radioactively labeled nucleic acid fragments with a sequencing gel, comprising:	Support for a method of determining the sequence of a nucleic acid of interest can be found, for instance, on page 84, 2nd ¶, which states that the signaling molecules of the invention are "particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Detecting nucleic acid fragments on a sequencing gel necessarily involves determining the sequence of the fragment.
providing or generating detectable non-radioactively labeled nucleic acid fragments,	Providing and generating labeled nucleic acid fragments complementary to the nucleic acid of interest is thoroughly discussed throughout the entire specification. In particular, U.S. Ser. No. 255,233 which eventually became the Ward Patents (e.g. 5,476,928 etc.), is incorporated in its entirety on pages 2 through 49 and is directed to non-radioactively labeled nucleic acid

Claim	Support in Specification
	fragments and their complements. *See also, e.g.,* the Abstract; page 6, final ¶; page 18, final ¶ through page 19, top ¶; page 28, first full ¶ through page 38, final ¶.
wherein each of said fragments comprises one or more nucleotides, and wherein said one or more nucleotides comprise one or more fluorescent indicators;	The specification provides support for nucleic acid fragments which have incorporated nucleotides labeled by one or more non-radioactive indicator molecules, *e.g.,* fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and	Literal support for "sequencing gel" may be found on page 84, 2nd ¶: "This Type of self-signaling molecule can be used to monitor any nucleic acid hybridization reaction. It is particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the specification provides support for sequencing gel, *e.g.,* page 84, which necessarily involves separating and resolving nucleic acid fragments.
detecting non-radioactively said separated or resolved fragments by detecting the fluorescent indicators.	Detecting the presence of the fragments is disclosed throughout the entire specification, such as in the Abstract, page 6 (penultimate ¶), page 84 (2nd ¶), page 93 through page 95, and original Claims 1, 7, 141, 142 and 168. The specification also provides support for detecting the nucleic acids by means of fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
Claim 1783. A process for resolving or separating non-radioactively labeled nucleic acid	Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the

Claim	Support in Specification
fragments with a sequencing gel, comprising:	specification provides support for sequencing gel, *e.g.,* page 84, which necessarily involves separating and resolving nucleic acid fragments.
providing or generating detectable non-radioactively labeled nucleic acid fragments comprising one or more nucleotides that can be attached to, or coupled to, or incorporated into DNA or RNA, and	Providing and generating labeled nucleic acid fragments complementary to the nucleic acid of interest is thoroughly discussed throughout the entire specification. In particular, U.S. Ser. No. 255,233 which eventually became the Ward Patents (e.g. 5,476,928 etc.), is incorporated in its entirety on pages 2 through 49 and is directed to non-radioactively labeled nucleic acid fragments and their complements. *See also, e.g.,* the Abstract; page 6, final ¶; page 18, final ¶ through page 19, top ¶; page 28, first full ¶ through page 38, final ¶.
wherein one or more fluorescent indicators are covalently attached, directly or through a linkage group, to said one or more nucleotides;	The specification provides support for nucleic acid fragments which have incorporated nucleotides labeled by one or more non-radioactive indicator molecules, *e.g.,* fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133. Furthermore, the specification provides specific support for attachment of fluorescent indicator molecules "directly or through a chemical linkage or linker arm to the nucleotide" on page 96, last paragraph to page 97 1st full paragraph. *See also, e.g.,* page 95, 1st ¶; and page 96, 1st ¶ ("The nucleotides are then modified...by having covalently attached thereto, to the P moiety and or the S moiety and/or the B moiety, a chemical moiety Sig.").
subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and	Literal support for "sequencing gel" may be found on page 84, 2nd ¶: "This Type of self-signaling molecule can be used to monitor any nucleic acid hybridization reaction. It is particularly important for detecting nucleic acids in gels (for example, sequencing gels)." Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the specification provides support for sequencing gel, *e.g.,* page 84, which necessarily involves separating and resolving nucleic acid fragments.

Claim	Support in Specification
detecting non-radioactively said separated or resolved fragments by means of said fluorescent indicators attached to said one or more nucleotides.	Detecting the presence of the fragments is disclosed throughout the entire specification, such as in the Abstract, page 6 (penultimate ¶), page 84 (2nd ¶), page 93 through page 95, and original Claims 1, 7, 141, 142 and 168. The specification also provides support for detecting the nucleic acids by means of fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
Claim 1795. A process for determining the sequence of a nucleic acid of interest comprising:	Support for a method of determining the sequence of a nucleic acid of interest can be found, for instance, on page 84, 2nd ¶, which states that the signaling molecules of the invention are "particularly important for detecting nucleic acids in gels (for example, sequencing gels)."
providing or generating detectable non-radioactively labeled nucleic acid fragments comprising: (a) a sequence complementary to said nucleic acid of interest or a portion thereof, and (b) fluorescent labels covalently attached, directly or through a linkage group, to said fragments;	The specification provides support for detectable nucleic acid fragments labeled by one or more non-radioactive indicator molecules, *e.g.,* fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133. The specification discloses that the DNA and RNA probes comprise a nucleotide sequence substantially matching the nucleic acid sequence of interest and upon localization of the probe to the nucleic acid sequence of interest the resulting hybrid can be observed and identified. *See, e.g.,* page 98, final ¶ through page 100, 1st ¶. The specification also provides specific support for attachment of fluorescent indicator molecules "directly or through a chemical linkage or linker arm to the nucleotide" on page 96, last paragraph to page 97 1st full paragraph. *See also, e.g.,* page 95, 1st ¶; and page 96, 1st ¶ ("The nucleotides are then modified…by having covalently attached thereto, to the P moiety and or the S moiety and/or the B moiety, a chemical moiety Sig.").
subjecting said labeled fragments to a	Separating and resolving are disclosed throughout the specification. For instance, the term

Claim	Support in Specification
sequencing gel to separate or resolve said labeled fragments;	"resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the specification provides support for "sequencing gel," *e.g.,* page 84, which necessarily involves separating and resolving nucleic acid fragments.
detecting non-radioactively said separated or resolved fragments by means of said attached fluorescent labels; and	Detecting the presence of the fragments is disclosed throughout the entire specification, such as in the Abstract, page 6 (penultimate ¶), page 84 (2nd ¶), page 93 through page 95, and original Claims 1, 7, 141, 142 and 168. The specification also provides support for detecting the nucleic acids by means of fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
determining the sequence of said nucleic acid of interest from said detected fragments.	The specification provides support for detecting fragments on a sequencing gel, *e.g.,* page 84, which necessarily includes determining the sequence of the fragments.
Claim 1796. A process for determining the sequence of a nucleic acid of interest comprising:	Support for a method of determining the sequence of a nucleic acid of interest can be found, for instance, on page 84, 2nd ¶, which states that the signaling molecules of the invention are "particularly important for detecting nucleic acids in gels (for example, sequencing gels)."
providing or generating detectable non-radioactively labeled nucleic acid fragments comprising: (a) a sequence complementary to said nucleic acid of interest or a portion thereof, and (b) different fluorescent labels covalently attached, directly or through a linkage	The specification provides support for detectable nucleic acid fragments labeled by one or more non-radioactive indicator molecules, *e.g.,* fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133. The specification discloses that the DNA and RNA probes comprise a nucleotide sequence substantially matching the nucleic acid sequence of interest and upon localization of the probe to the nucleic acid sequence of interest the resulting hybrid can be observed and identified. *See, e.g.,*

Claim	Support in Specification
group, to said fragments;	page 98, final ¶ through page 100, 1st ¶. "Different" fluorescent labels are specifically disclosed on page 48, 1st ¶, "If necessary, two sets of labels can be used -- one which would be specific for chromosome 23 and one for some other chromosome. By measuring in each cell the ratio of the two labels, which might be of different colors, it is possible to identify the cells which show an abnormal number of chromosomes number 23." *See also*, Example 9 on pages 46 through 47, and original Claims 42, 43, 88, 89, and 130-133 that claim fluorescein, rhodamine and dansyl. Furthermore, the specification provides specific support for attachment of fluorescent indicator molecules "directly or through a chemical linkage or linker arm to the nucleotide" on page 96, last paragraph to page 97 1st full paragraph. *See also, e.g.,* page 95, 1st ¶; and page 96, 1st ¶ ("The nucleotides are then modified...by having covalently attached thereto, to the P moiety and or the S moiety and/or the B moiety, a chemical moiety Sig.").
subjecting said labeled fragments to a sequencing gel to separate or resolve said labeled fragments;	Separating and resolving are disclosed throughout the specification. For instance, the term "resolving" or "resolution" appear on pages 31 (1st full ¶) and 33 (1st full ¶). Furthermore, the specification provides support for "sequencing gel," *e.g.,* page 84, which necessarily involves separating and resolving nucleic acid fragments.
detecting non-radioactively said separated or resolved fragments by means of said attached different fluorescent labels; and	Detecting the presence of the fragments is disclosed throughout the entire specification, such as in the Abstract, page 6 (penultimate ¶), page 84 (2nd ¶), page 93 through page 95, and original Claims 1, 7, 141, 142 and 168. The specification also provides support for detecting the nucleic acids by means of fluorescent dyes, including fluorescein, rhodamine and dansyl. *See, e.g.,* page 26, 1st ¶; example 9 on pages 46 through 47; page 96, last ¶ through page 97 1st ¶, and original Claims 42, 43, 88, 89, and 130-133.
determining the sequence of said nucleic acid of interest from said detected fragments.	The specification provides support for detecting fragments on a sequencing gel, *e.g.,* page 84, which necessarily includes determining the sequence of the fragments.